REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 52-68, 72, 74-94, 98, 100-103, and 113 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The examiner finds the oath or declaration defective and requires a new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date.

Attached hereto is a substitute declaration executed by three of the original four inventors. For the record, the reason the substitute declaration is signed by only Lydia Avivi, Aviva Dotan, and Yehoshua Ravia but not by Rafi Korenstein is that inventorship is now corrected by a Petition to Correct Inventorship Under 37 CFR §1.48(b) filed June 19, 2003, a copy of which is attached hereto, to delete Rafi Korenstein as an inventor in the present application due to amendment of the claims, including cancellation of the originally filed claims in the preliminary amendment filed June 5, 2002.

Claims 68, 71, 94, and 97 have been objected to as being dependent upon a rejected base claim but would be allowable

if rewritten in independent form including all the limitations of the base claim and any intervening claims. Claims 71 and 97 are cancelled and claims 68 and 94 are now rewritten in independent form to include all the limitations of the base claim and any intervening claims. Accordingly, claims 68 and 94 are in condition for allowance.

Claims 52-67, 69, 70, 72-93, 95, 96, 98-103, and 113 have been rejected under 35 U.S.C. §102(e) as being anticipated by Feinberg (U.S. 6,235,474). The examiner states that Feinberg discloses a method comprising obtaining a normal biological sample from a subject, and screening said sample for abnormal imprinting in at least one gene wherein abnormal imprinting indicates the presence of disease. The examiner takes the position that, based on the definition of imprinting in column 8, lines 6-13, and also in other references of record, "imprinting" appears to refer to the same phenomenon as "synchrony" and "asynchrony" in the instant application. This rejection is respectfully traversed.

The claims are now amended to exclude imprinted loci which replicate asynchronouly in normal diploid cells from the presently claimed method, thereby obviating this anticipation rejection because Feinberg only discloses or teaches using loci/ genes subject to imprinting in his diagnostic method.

Furthermore, with due respect to the examiner, the examiner has confused "imprinting" with the general phenomenon of "synchrony" and "asynchrony". To clarify, applicants provide below an explanation of the difference.

Feinberg defines genomic imprinting at column 8, lines 6-9, as follows:

> Genomic imprinting is an epigenetic modification of a specific parental chromosome in the gamete or zygote that leads to monoallelic or differential expression of two alleles of a gene in somatic cells of the offspring. (emphasis added)

It is well known in the art that imprinted genes are only a small subset of the monoallelically-expressed genes, although they retain the characteristics of the group as a whole, in which there are differences between the two allelic counterparts (alleles) in (i) expression capability, (ii) epigenetic profiles (methylation capacity, chromatin conformation, etc.), and (iii) replication timing (asynchronous replication). Attached hereto are copies of a review by Goren and Cedar, *Nature Reviews Molecular Cell Biology*, 4:25-32, 2003 (see page 26, right column to page 29, left column) and Singh et al., *Nature Genetics* 33:349-351 (1-3), 2003 (see first paragraph on page 349 (page 1 of online version)), which discloses that:

> Monoallelically expressed genes fall into three distinct classes. X-inactivation in

> female cells is a random process resulting in half of the cells choosing the maternal X chromosome and half choosing the paternal X chromosome. By contrast, autosomal imprinted genes such as Igf2 and H19 are monoallelically expressed according to the parent of origin. The third class, randomly monoallelically transcribed autosomal genes, includes the large family of odorant receptor genes, as well as genes encoding the immunoglobulins, T-cell receptors, interleukins, natural killer-cell receptors and pheromone receptors. (emphasis added)

Clearly, the monoallelically expressed imprinted genes are distinct from the other two classes of monoallelically expressed genes, the genes/loci on X-chromosome in female individuals (X-chromosome inactivation) and the genes/loci subjected to allelic exclusion (randomly monoallelically transcribed autosomal genes). Accordingly, claims 72 and 98, which are limited to two classes of monoallelically expressed non-imprinted genes cannot be anticipated by Feinberg.

Moreover, it is clear that the loss of monoallelic expression is accompanied by loss of the characteristics of monoalleic expression, which in the case of replication timing is displayed by release of asynchrony (synchronous replication). Yet, a gene undergoing a change from an asynchronous mode of replication to a synchronous one as a result of some pathological conditions in somatic cells of an organism is not defined as an imprinted gene. Similarly, loss of biallelic expression in

somatic cells due to malignancy, observed by a shift from a synchronous mode of allelic replication to an asynchronous mode, does not define the gene, which undergoes this somatic change, as an imprinted gene.

A more recent definition of genomic imprinting on page 392, middle column, of Feinberg, PNAS 98(2):392-394 (2001), a copy of which is attached hereto, is consistent with the definition in Feinberg, U.S. Patent 6,235,474, but further clarifies that the epigenetic modification is of a specific parental allele of a gene, or the chromosome on which it resides, in the gamete or zygote. It is apparent that genomic imprinting involves parent-of-origin-dependent differences in the expression of two alleles of a gene or, in other words, genomic imprinting leads to monoallelic expression (allele-specific expression) depending on the parent of origin of the allele. Furthermore, the parent-of-origin allele-specific modification of an imprinted gene is established and initiated, by definition, in early developmental stages, gamete or zygote, and not in late post-natal somatic cells. Therefore, loss of biallelic expression (loss of synchrony) cannot be construed to be imprinting that is "abnormally on", if this is what is interpreted by the examiner.

In the same middle column, page 392 of the attached Feinberg, PNAS (2001) paper, immediately following the definition

of genomic imprinting, Feinberg further teaches that "[loss of imprinting] LOI involves loss of the normal pattern of expression of specific parental allele, and in cancer it can lead to activation of growth-promoting imprinted genes such as insulin-like growth-factor II, as well as silencing of potential [imprinted] tumor suppressor genes such as p57 and ARH1" (underlining and bracketing added). Accordingly, it is clear to those of ordinary skill in the art that both the phenomena of "abnormally on" or "abnormally off" imprinting are taken as abnormal imprinting (loss of imprinting), the first of which is involved with activation of a silenced allele and is described as "abnormally on", whereas the second, which is associated with silencing of an active allele, is referred to as "abnormally off". Undoubtedly, both terms "abnormally on" and "abnormally off" were used in the cited and applied Feinberg reference to describe loss of imprinting, and as such, define only abnormalities in imprinted genes as would be readily understood by those of skill in the art.

In short, for the reasons discussed above, the cited and applied Feinberg not only does not anticipate the loss of asynchrony (monallelic expression of loci subject to X-chromosome inactivation in female individuals or to allelic exclusion) as positively recited in claims 72, 98 and 113, but also does not

anticipate the loss of synchrony as recited in claim 113 and in claims dependent therefrom.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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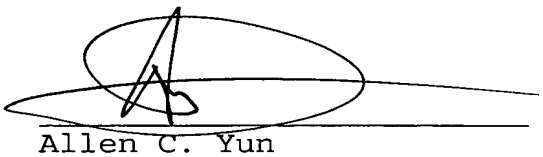
By 
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